# WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Friday, December 21, 2007

| Hide? | Set Name | Query | Hit Count |
|---|---|---|---|
| | | *DB=PGPB; THES=ASSIGNEE; PLUR=YES; OP=ADJ* | |
| ☐ | L2 | (non adj ribosomal peptide (synthetase or synthase) or NRPS) same (polyketide synthase or pks) same linker | 10 |
| | | *DB=USPT,USOC,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ* | |
| ☐ | L1 | (non adj ribosomal peptide (synthetase or synthase) or NRPS) same (polyketide synthase or pks) same linker | 4 |

END OF SEARCH HISTORY

FILE 'HOME' ENTERED AT 10:40:31 ON 21 DEC 2007

=> s polyketide synthase and nonribosomal peptide synthase and linker
L1 0 FILE MEDLINE
L2 1 FILE CAPLUS
L3 0 FILE SCISEARCH
L4 2 FILE LIFESCI
L5 1 FILE BIOSIS
L6 0 FILE EMBASE

TOTAL FOR ALL FILES
L7 4 POLYKETIDE SYNTHASE AND NONRIBOSOMAL PEPTIDE SYNTHASE AND LINKER

=> d ibib abs

L7 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:737868 CAPLUS Full-text
DOCUMENT NUMBER: 139:257289
TITLE: Methods to mediate polyketide synthase module effectiveness
INVENTOR(S): Gokhale, Rajesh S.; Tsuji, Stuart; Khosla, Chaitan; Wu, Nicholas; Cane, David E.
PATENT ASSIGNEE(S): The Board of Trustees of the Leland Stanford Junior University, USA; Brown University Research Foundation
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 2003076581 | A2 | 20030918 | WO 2003-US6910 | | 20030304 |
| WO 2003076581 | A3 | 20050210 | | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | | |
| US 2003068676 | A1 | 20030410 | US 2002-91244 | | 20020304 |
| US 7001748 | B2 | 20060221 | | | |
| AU 2003213757 | A1 | 20030922 | AU 2003-213757 | | 20030304 |
| US 2006110789 | A1 | 20060525 | US 2005-506630 | | 20050401 |
| PRIORITY APPLN. INFO.: | | | US 2002-361758P | P | 20020304 |
| | | | US 2002-91244 | A | 20020304 |
| | | | US 1999-119363P | P | 19990209 |
| | | | US 2000-500747 | A2 | 20000209 |
| | | | US 2001-272985P | P | 20010302 |
| | | | US 2001-272987P | P | 20010302 |
| | | | WO 2003-US6910 | W | 20030304 |

AB Linking sequences which modulate cross-talk between modules of Type I polyketide synthases have been identified. Thus, arbitrarily chosen modules can be mixed and matched by supplying the appropriate linkers to obtain desired polyketide synthases and new polyketides. The modules are provided suitable linkers so that the polyketide chain is passed from one module to the other in the correct sequence. Synthetic peptides which mimic linkers can be used to inhibit the synthesis of polyketides. Kinetic channeling, both intrapolypeptide and interpolypeptide, of diketide intermediates in a Type I polyketide synthase can occur. In addition, the role of protein-protein interactions between a donor acyl carrier protein (ACP) domain and a downstream ketosynthase (KS) domain and enzyme-substrate interactions in the channeling of intermediates between polyketide synthase modules and between a polyketide synthase module and a nonribosomal peptide synthase (NRPS) module has been identified.

=> d 2-4 ibib abs

L7 ANSWER 2 OF 4 LIFESCI COPYRIGHT 2007 CSA on STN

ACCESSION NUMBER: 2003:33402 LIFESCI Full-text
TITLE: Cloning and Characterization of the Bleomycin Biosynthetic Gene Cluster from Streptomyces verticillus ATCC15003
AUTHOR: Shen, B.; Du, L.; Sanchez, C.; Edwards, D.J.; Chen, Mei; Murrell, J.M.
CORPORATE SOURCE: Department of Chemistry, University of California, Davis, One Shields Avenue, Davis, CA 95616, USA
SOURCE: Journal of Natural Products [J. Nat. Prod.], (20020322) vol. 65, no. 3, pp. 422-431.
ISSN: 0163-3864.
DOCUMENT TYPE: Journal
FILE SEGMENT: J
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Bleomycin (BLM) biosynthesis has been studied as a model for hybrid peptide-polyketide natural product biosynthesis. Cloning, sequencing, and biochemical characterization of the blm biosynthetic gene cluster from Streptomyces verticillus ATCC15003 revealed that (1) the BLM hybrid peptide-polyketide aglycon is assembled by the BLM megasynthetase that consists of both nonribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) modules; (2) BlmIX/BlmVIII/BlmVII constitute a natural hybrid NRPS/PKS/NRPS system, serving as a model for both hybrid NRPS/PKS and PKS/NRPS systems; (3) the catalytic sites appear to be conserved in both hybrid NRPS/PKS and nonhybrid NRPS or PKS systems, with the exception of the KS domains in the hybrid NRPS /PKS systems that are unique; (4) specific interpolypeptide linkers may play a critical role in intermodular communication to facilitate the transfer of the growing intermediates between the interacting NRPS and/or PKS modules; (5) post-translational modification of the BLM megasynthetase has been accomplished by a single PPTase with broad carrier protein specificity; and (6) BlmIV /BlmIII-templated assembly of the BLM bithiazole moiety requires intriguing protein juxtaposition and modular recognition. These results lay the foundation to investigate the molecular basis for intermodular communication between NRPS and PKS in hybrid peptide-polyketide natural product biosynthesis and set the stage for engineering novel BLM analogues by genetic manipulation of genes governing BLM biosynthesis.

L7 ANSWER 3 OF 4 LIFESCI COPYRIGHT 2007 CSA on STN
ACCESSION NUMBER: 2002:54206 LIFESCI Full-text
TITLE: The biosynthetic gene cluster for the anticancer drug bleomycin from Streptomyces verticillus ATCC15003 as a model for hybrid peptide-polyketide natural product biosynthesis
AUTHOR: Shen, B.; Du, L.; Sanchez, C.; Edwards, D.J.; Chen, M.; Murrell, J.M.
CORPORATE SOURCE: Department of Chemistry, University of California, One Shields Avenue, Davis, CA 95616, USA
SOURCE: Journal of Industrial Microbiology & Biotechnology [J. Ind. Microbiol. Biotechnol.], (20011200) vol. 27, no. 6, pp. 378-385.
ISSN: 1367-5435.
DOCUMENT TYPE: Journal
FILE SEGMENT: J; A; W2
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The hybrid peptide-polyketide backbone of bleomycin (BLM) is assembled by the BLM megasynthetase that consists of both nonribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) modules. BlmIX/BlmVIII/BlmVII constitute a natural hybrid NRPS/PKS/NRPS system, serving as a model for both hybrid NRPS/PKS and PKS/NRPS systems. Sequence analysis and functional comparison of domains and modules of BlmIX/BlmVIII/BlmVII with those of nonhybrid NRPS and PKS systems suggest that (1) the same catalytic sites appear to be conserved in both hybrid NRPS-PKS and nonhybrid NRPS or PKS systems, with the exception of the KS domains in the hybrid NRPS/PKS systems that are unique; (2) specific interpolypeptide linkers may play a critical role in intermodular communication to facilitate transfer of the growing intermediates between the interacting NRPS and/or PKS modules; and (3) posttranslational modification of the BLM megasynthetase has been accomplished by a single PPTase with a broad substrate specificity toward the apo forms of both acyl carrier proteins (ACPs) and peptidyl carrier proteins (PCPs).

L7 ANSWER 4 OF 4 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:285469 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200285469
TITLE: Quantitative analysis of the relative contributions of donor acyl carrier proteins, acceptor ketosynthases, and linker regions to intermodular transfer of intermediates in hybrid polyketide synthases.
AUTHOR(S): Wu, Nicholas; Cane, David E.; Khosla, Chaitan [Reprint author]

CORPORATE SOURCE: Department of Chemistry, Stanford University, Stanford, CA, 94305, USA
ck@chemeng.stanford.edu
SOURCE: Biochemistry, (April 16, 2002) Vol. 41, No. 15, pp. 5056-5066. print.
CODEN: BICHAW. ISSN: 0006-2960.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 8 May 2002
Last Updated on STN: 8 May 2002

AB 6-Deoxyerythronolide B synthase (DEBS) is the modular polyketide synthase (PKS) responsible for the biosynthesis of 6-dEB, the aglycon core of the antibiotic erythromycin. The biosynthesis of 6-dEB proceeds in an assembly-line fashion through the six modules of DEBS, each of which catalyzes a dedicated set of reactions, such that the structure of the final product is determined by the arrangement of modules along the assembly line. This transparent relationship between protein sequence and enzyme function is common to all modular PKSs and makes these enzymes an attractive scaffold for protein engineering through module swapping. One of the fundamental issues relating to module swapping that still needs to be addressed is the mechanism by which intermediates are channeled from one module to the next. While it has been previously shown that short linker regions at the N- and C-termini of adjacent polypeptides play an important role in mediating intermodular transfer, the contributions of other protein-protein interactions have not yet been probed. Here, we investigate the roles of the linker interactions as well as the interactions between the donor acyl carrier protein (ACP) domain and the downstream ketosynthase (KS) domain in various contexts. Linker interactions and ACP-KS interactions make relatively equal contributions at the module 2-module 3 and the module 4-module 5 interfaces in DEBS. In contrast, modules 2 and 6 are more tolerant toward substrates presented by nonnatural ACP domains. This tolerance was exploited for engineering hybrid PKS-PKS and PKS-NRPS (nonribosomal peptide synthetase) junctions and suggests fundamental ground rules for engineering novel chimeric PKSs in the future.

=> s polyketide synthase and non-ribosomal peptide synthase and linker

TOTAL FOR ALL FILES
L14 6 POLYKETIDE SYNTHASE AND NON-RIBOSOMAL PEPTIDE SYNTHASE AND LINKE
R

=> s l7 and l14
TOTAL FOR ALL FILES
L21 0 L7 AND L14

=> s l7 or l14
TOTAL FOR ALL FILES
L28 10 L7 OR L14

=> dup rem l28
PROCESSING COMPLETED FOR L28
L29 8 DUP REM L28 (2 DUPLICATES REMOVED)

=> d ibib abs 1-8

L29 ANSWER 1 OF 8 MEDLINE on STN
ACCESSION NUMBER: 2006042704 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16430229
TITLE: Heterologous production of epothilone C and D in Escherichia coli.
AUTHOR: Mutka Sarah C; Carney John R; Liu Yaoquan; Kennedy Jonathan
CORPORATE SOURCE: Kosan Biosciences, Inc., 3832 Bay Center Place, Hayward, California 94545, USA.
SOURCE: Biochemistry, (2006 Jan 31) Vol. 45, No. 4, pp. 1321-30.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200604
ENTRY DATE: Entered STN: 25 Jan 2006
Last Updated on STN: 15 Apr 2006
Entered Medline: 14 Apr 2006

AB The epothilones are a family of polyketide natural products that show a high potential as anticancer drugs. They are synthesized by the action of a hybrid nonribosomal peptide synthetase/polyketide synthase in the myxobacterium Sorangium cellulosum. In this work, the genes

encoding the entire cluster,epoA, epoB, epoC, epoD, epoE, and epoF, were redesigned and synthesized to allow for expression in Escherichia coli. The expression of the largest of the proteins, EpoD, also required the protein be separated into two polypeptides with compatible module linkers. Using a combination of lowered temperature, chaperone coexpression, and alternative promoters, we succeeded in producing a soluble protein from all genes in the epothilone cluster. The entire synthetic epothilone cluster was then expressed in a strain of E. coli modified to enable polyketide biosynthesis, resulting in the production of epothilones C and D. Furthermore, feeding a thioester of the normal substrate for EpoD to cells expressing the epoD, epoE, and epoF genes also led to the production of epothilones C and D. The design of the synthetic epothilone genes together with E. coli expression provides the ideal platform for both the biochemical investigation of the epothilone PKS and the generation of novel biosynthetic epothilone analogues.

L29 ANSWER 2 OF 8 MEDLINE on STN
ACCESSION NUMBER: 2004583519 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15556004
TITLE: Hybrid nonribosomal peptide-polyketide interfaces in epothilone biosynthesis: minimal requirements at N and C termini of EpoB for elongation.
AUTHOR: Liu Fei; Garneau Sylvie; Walsh Christopher T
CORPORATE SOURCE: Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, 240 Longwood Avenue, Boston, MA 02115, USA.
CONTRACT NUMBER: GM21643 (NIGMS)
GM66456 (NIGMS)
SOURCE: Chemistry & biology, (2004 Nov) Vol. 11, No. 11, pp. 1533-42.
Journal code: 9500160. ISSN: 1074-5521.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200504
ENTRY DATE: Entered STN: 24 Nov 2004
Last Updated on STN: 26 Apr 2005
Entered Medline: 25 Apr 2005

AB Epothilone (Epo) D, an antitumor agent currently in clinical trials, is a hybrid natural product produced by the combined action of nonribosomal peptide synthetases (NRPS) and polyketide synthases (PKS). In the epothilone biosynthetic pathway, EpoB, a 165 kDa NRPS is inserted into an otherwise entirely PKS assembly line, forming two hybrid NRPS-PKS interfaces. In light of the terminal linker effect previously identified in PKS, the N- and C-terminal sequences of EpoB were examined for their roles in propagating the incipient natural product. Eight amino acid residues at EpoB C terminus, in which six are positively charged, were found to be a key component of the C-terminal linker effect. A minimal sequence of 56 residues at EpoB N terminus was required for elongating the acetyl group from the acyl carrier protein (ACP) of EpoA to form methylthiazolyl-S-EpoB.

L29 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:737868 CAPLUS Full-text
DOCUMENT NUMBER: 139:257289
TITLE: Methods to mediate polyketide synthase module effectiveness
INVENTOR(S): Gokhale, Rajesh S.; Tsuji, Stuart; Khosla, Chaitan; Wu, Nicholas; Cane, David E.
PATENT ASSIGNEE(S): The Board of Trustees of the Leland Stanford Junior University, USA; Brown University Research Foundation
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003076581 | A2 | 20030918 | WO 2003-US6910 | 20030304 |
| WO 2003076581 | A3 | 20050210 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,

UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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|---|---|---|---|---|---|
| US 2003068676 | A1 | 20030410 | US 2002-91244 | | 20020304 |
| US 7001748 | B2 | 20060221 | | | |
| AU 2003213757 | A1 | 20030922 | AU 2003-213757 | | 20030304 |
| US 2006110789 | A1 | 20060525 | US 2005-506630 | | 20050401 |
| PRIORITY APPLN. INFO.: | | | US 2002-361758P | P | 20020304 |
| | | | US 2002-91244 | A | 20020304 |
| | | | US 1999-119363P | P | 19990209 |
| | | | US 2000-500747 | A2 | 20000209 |
| | | | US 2001-272985P | P | 20010302 |
| | | | US 2001-272987P | P | 20010302 |
| | | | WO 2003-US6910 | W | 20030304 |

AB Linking sequences which modulate cross-talk between modules of Type I polyketide synthases have been identified. Thus, arbitrarily chosen modules can be mixed and matched by supplying the appropriate linkers to obtain desired polyketide synthases and new polyketides. The modules are provided suitable linkers so that the polyketide chain is passed from one module to the other in the correct sequence. Synthetic peptides which mimic linkers can be used to inhibit the synthesis of polyketides. Kinetic channeling, both intrapolypeptide and interpolypeptide, of diketide intermediates in a Type I polyketide synthase can occur. In addition, the role of protein-protein interactions between a donor acyl carrier protein (ACP) domain and a downstream ketosynthase (KS) domain and enzyme-substrate interactions in the channeling of intermediates between polyketide synthase modules and between a polyketide synthase module and a nonribosomal peptide synthase (NRPS) module has been identified.

L29 ANSWER 4 OF 8 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:285469 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200285469
TITLE: Quantitative analysis of the relative contributions of donor acyl carrier proteins, acceptor ketosynthases, and linker regions to intermodular transfer of intermediates in hybrid polyketide synthases.
AUTHOR(S): Wu, Nicholas; Cane, David E.; Khosla, Chaitan [Reprint author]
CORPORATE SOURCE: Department of Chemistry, Stanford University, Stanford, CA, 94305, USA
ck@chemeng.stanford.edu
SOURCE: Biochemistry, (April 16, 2002) Vol. 41, No. 15, pp. 5056-5066. print.
CODEN: BICHAW. ISSN: 0006-2960.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 8 May 2002
Last Updated on STN: 8 May 2002

AB 6-Deoxyerythronolide B synthase (DEBS) is the modular polyketide synthase (PKS) responsible for the biosynthesis of 6-dEB, the aglycon core of the antibiotic erythromycin. The biosynthesis of 6-dEB proceeds in an assembly-line fashion through the six modules of DEBS, each of which catalyzes a dedicated set of reactions, such that the structure of the final product is determined by the arrangement of modules along the assembly line. This transparent relationship between protein sequence and enzyme function is common to all modular PKSs and makes these enzymes an attractive scaffold for protein engineering through module swapping. One of the fundamental issues relating to module swapping that still needs to be addressed is the mechanism by which intermediates are channeled from one module to the next. While it has been previously shown that short linker regions at the N- and C-termini of adjacent polypeptides play an important role in mediating intermodular transfer, the contributions of other protein-protein interactions have not yet been probed. Here, we investigate the roles of the linker interactions as well as the interactions between the donor acyl carrier protein (ACP) domain and the downstream ketosynthase (KS) domain in various contexts. Linker interactions and ACP-KS interactions make relatively equal contributions at the module 2-module 3 and the module 4-module 5 interfaces in DEBS. In contrast, modules 2 and 6 are more tolerant toward substrates presented by nonnatural ACP domains. This tolerance was exploited for engineering hybrid PKS-PKS and PKS-NRPS (nonribosomal peptide synthetase) junctions and suggests fundamental ground rules for engineering novel chimeric PKSs in the future.

L29 ANSWER 5 OF 8 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2002177295 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11908996
TITLE: Cloning and characterization of the bleomycin biosynthetic gene cluster from Streptomyces verticillus ATCC15003.

AUTHOR: Shen Ben; Du Liangcheng; Sanchez Cesar; Edwards Daniel J; Chen Mei; Murrell Jeffrey M
CORPORATE SOURCE: Department of Chemistry, University of California, Davis, One Shields Avenue, Davis, California 95616, USA.. bshen@pharmacy.wisc.edu
CONTRACT NUMBER: AI40475 (NIAID)
GM07377 (NIGMS)
SOURCE: Journal of natural products, (2002 Mar) Vol. 65, No. 3, pp. 422-31. Ref: 35
Journal code: 7906882. ISSN: 0163-3864.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 24 Mar 2002
Last Updated on STN: 12 Jun 2002
Entered Medline: 11 Jun 2002

AB Bleomycin (BLM) biosynthesis has been studied as a model for hybrid peptide-polyketide natural product biosynthesis. Cloning, sequencing, and biochemical characterization of the blm biosynthetic gene cluster from Streptomyces verticillus ATCC15003 revealed that (1) the BLM hybrid peptide-polyketide aglycon is assembled by the BLM megasynthetase that consists of both nonribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) modules; (2) BlmIX/BlmVIII/BlmVII constitute a natural hybrid NRPS/PKS/NRPS system, serving as a model for both hybrid NRPS/PKS and PKS/NRPS systems; (3) the catalytic sites appear to be conserved in both hybrid NRPS/PKS and nonhybrid NRPS or PKS systems, with the exception of the KS domains in the hybrid NRPS/PKS systems that are unique; (4) specific interpolypeptide linkers may play a critical role in intermodular communication to facilitate the transfer of the growing intermediates between the interacting NRPS and/or PKS modules; (5) post-translational modification of the BLM megasynthetase has been accomplished by a single PPTase with broad carrier protein specificity; and (6) BlmIV/BlmIII-templated assembly of the BLM bithiazole moiety requires intriguing protein juxtaposition and modular recognition. These results lay the foundation to investigate the molecular basis for intermodular communication between NRPS and PKS in hybrid peptide-polyketide natural product biosynthesis and set the stage for engineering novel BLM analogues by genetic manipulation of genes governing BLM biosynthesis.

L29 ANSWER 6 OF 8 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2002051155 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11774003
TITLE: The biosynthetic gene cluster for the anticancer drug bleomycin from Streptomyces verticillus ATCC15003 as a model for hybrid peptide-polyketide natural product biosynthesis.
AUTHOR: Shen B; Du L; Sanchez C; Edwards D J; Chen M; Murrell J M
CORPORATE SOURCE: Department of Chemistry, University of California, Davis, One Shields Avenue, Davis, CA 95616, USA.
CONTRACT NUMBER: AI40475 (NIAID)
T32GM07377 (NIGMS)
SOURCE: Journal of industrial microbiology & biotechnology, (2001 Dec) Vol. 27, No. 6, pp. 378-85. Ref: 31
Journal code: 9705544. ISSN: 1367-5435.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 25 Jan 2002
Last Updated on STN: 21 Feb 2002
Entered Medline: 20 Feb 2002

AB The hybrid peptide-polyketide backbone of bleomycin (BLM) is assembled by the BLM megasynthetase that consists of both nonribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) modules. BlmIX/BlmVIII/BlmVII constitute a natural hybrid NRPS/PKS/NRPS system, serving as a model for both hybrid NRPS/PKS and PKS/NRPS systems. Sequence analysis and functional comparison of domains and modules of BlmIX/BlmVIII/BlmVII with those of nonhybrid NRPS and PKS systems suggest that (1) the same catalytic sites appear to be conserved in both hybrid NRPS-PKS and nonhybrid NRPS or PKS systems, with the exception of the KS domains in the hybrid NRPS/PKS systems that are unique; (2) specific interpolypeptide linkers may play a critical role in intermodular communication to facilitate transfer of the growing intermediates between the interacting NRPS

and/or PKS modules; and (3) posttranslational modification of the BLM megasynthetase has been accomplished by a single PPTase with a broad substrate specificity toward the apo forms of both acyl carrier proteins (ACPs) and peptidyl carrier proteins (PCPs).

L29 ANSWER 7 OF 8 MEDLINE on STN
ACCESSION NUMBER: 2001293979 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11378961
TITLE: Biosynthesis of hybrid peptide-polyketide natural products.
AUTHOR: Du L; Shen B
CORPORATE SOURCE: Department of Chemistry, University of California at Davis, One Shields Avenue, Davis, CA 95616, USA..
shen@chem.ucdavis.edu
CONTRACT NUMBER: AI40475 (NIAID)
CA78747 (NCI)
SOURCE: Current opinion in drug discovery & development, (2001 Mar) Vol. 4, No. 2, pp. 215-28. Ref: 56
Journal code: 100887519. ISSN: 1367-6733.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 22 Oct 2001
Last Updated on STN: 22 Oct 2001
Entered Medline: 18 Oct 2001

AB The structural and catalytic similarities between non-ribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) support the idea of combining individual NRPS and PKS modules for combinatorial biosynthesis. Recent advances in cloning and characterization of biosynthetic gene clusters for naturally occurring hybrid polyketide-peptide metabolites have provided direct evidence for the existence of hybrid NRPS-PKS systems, thus setting the stage to investigate the molecular basis for intermodular communication between NRPS and PKS modules. Reviewed in this article are biosynthetic data pertinent to hybrid peptide-polyketide biosynthesis published up to late 2000. Hybrid peptide-polyketide natural products can be divided into two classes: (i) those whose biosyntheses do not involve functional interaction between NRPS and PKS modules; and (ii) those whose biosyntheses are catalyzed by hybrid NRPS-PKS systems involving direct interactions between NRPS and PKS modules. It is the latter systems that are most likely amenable to combinatorial biosynthesis. The same catalytic sites appear to be conserved in both hybrid NRPS-PKS and normal NRPS or PKS systems, with the exception of the ketoacyl synthase domains in hybrid NRPS-PKS systems which are unique. Specific linkers may play a critical role in communication, facilitating the transfer of the growing intermediates between the interacting NRPS and/or PKS modules. In addition, phosphopantetheinyl transferases with broad carrier protein specificity are essential for the production of functional hybrid NRPS-PKS megasynthetases. These findings should now be taken into consideration in engineered biosynthesis of hybrid peptide-polyketide natural products for drug discovery and development.

L29 ANSWER 8 OF 8 MEDLINE on STN
ACCESSION NUMBER: 2001301512 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11162234
TITLE: Hybrid peptide-polyketide natural products: biosynthesis and prospects toward engineering novel molecules.
AUTHOR: Du L; Sanchez C; Shen B
CORPORATE SOURCE: Department of Chemistry, University of California, One Shields Avenue, Davis, California 95616, USA.
CONTRACT NUMBER: AI40475 (NIAID)
CA78747 (NCI)
SOURCE: Metabolic engineering, (2001 Jan) Vol. 3, No. 1, pp. 78-95.
Ref: 66
Journal code: 9815657. ISSN: 1096-7176.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 4 Jun 2001
Last Updated on STN: 4 Jun 2001
Entered Medline: 31 May 2001

AB The structural and catalytic similarities between modular nonribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) inspired us to search for hybrid NRPS-PKS systems. By examining the biochemical and genetic data known to date for the biosynthesis of hybrid peptide-polyketide natural products, we show (1) that the same catalytic sites are conserved between the hybrid NRPS-PKS and normal NRPS or PKS systems, although the ketoacyl synthase domain in NRPS/PKS hybrids is unique, and (2) that specific interpolypeptide linkers exist at both the C- and N-termini of the NRPS and PKS proteins, which presumably play a critical role in facilitating the transfer of the growing peptide or polyketide intermediate between NRPS and PKS modules in hybrid NRPS-PKS systems. These findings provide new insights for intermodular communications in hybrid NRPS-PKS systems and should now be taken into consideration in engineering hybrid peptide-polyketide biosynthetic pathways for making novel "unnatural" natural products. Copyright 2001 Academic Press.

=> s polyketide synthase and hybrid and linker
TOTAL FOR ALL FILES
L36 55 POLYKETIDE SYNTHASE AND HYBRID AND LINKER

=> dup rem 136
PROCESSING COMPLETED FOR L36
L37 14 DUP REM L36 (41 DUPLICATES REMOVED)

=> d ibib abs 1-14

L37 ANSWER 1 OF 14 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2007438213 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17656315
TITLE: Structure-based dissociation of a type I polyketide synthase module.
AUTHOR: Chen Alice Y; Cane David E; Khosla Chaitan
CORPORATE SOURCE: Department of Chemical Engineering, Stanford University, Stanford, CA 94305, USA.
CONTRACT NUMBER: CA 66736 (United States NCI)
GM 22172 (United States NIGMS)
SOURCE: Chemistry & biology, (2007 Jul) Vol. 14, No. 7, pp. 784-92.
Journal code: 9500160. ISSN: 1074-5521.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200712
ENTRY DATE: Entered STN: 28 Jul 2007
Last Updated on STN: 14 Dec 2007
Entered Medline: 13 Dec 2007
AB Individual modules of modular polyketide synthases (PKSs) such as 6-deoxyerythronolide B synthase (DEBS) consist of conserved, covalently linked domains separated by unconserved intervening linker sequences. To better understand the protein-protein and enzyme-substrate interactions in modular catalysis, we have exploited recent structural insights to prepare stand-alone domains of selected DEBS modules. When combined in vitro, ketosynthase (KS), acyl transferase (AT), and acyl carrier protein (ACP) domains of DEBS module 3 catalyzed methylmalonyl transfer and diketide substrate elongation. When added to a minimal PKS, ketoreductase domains from DEBS modules 1, 2, and 6 showed specificity for the beta-ketoacylthioester substrate, but not for either the ACP domain carrying the polyketide substrate or the KS domain that synthesized the substrate. With insights into catalytic efficiency and specificity of PKS modules, our results provide guidelines for constructing optimal hybrid PKS systems.

L37 ANSWER 2 OF 14 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:335441 BIOSIS Full-text
DOCUMENT NUMBER: PREV200600339897
TITLE: Methods of making polyketides using hybrid polyketide synthases.
AUTHOR(S): Gokhale, Rajesh S. [Inventor]; Tsuji, Stuart [Inventor]; Khosla, Chaitan [Inventor]
CORPORATE SOURCE: New Delhi, India
ASSIGNEE: The Board of Trustees of the Leland Stanford Junior University
PATENT INFORMATION: US 07001748 20060221
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (FEB 21 2006)
CODEN: OGUPE7. ISSN: 0098-1133.

DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Jul 2006
Last Updated on STN: 5 Jul 2006

AB Linking sequences which modulate cross-talk between modules of Type I polyketide synthases have been identified. Thus, arbitrarily chosen modules can be mixed and matched by supplying the appropriate linkers to obtain desired polyketide synthases and new polyketides. The modules are provided suitable linkers so that the polyketide chain is passed from one module to the other in the correct sequence. Synthetic peptides which mimic linkers can be used to inhibit the synthesis of polyketides. Kinetic channeling, both intrapolypeptide and interpolypeptide, of diketide intermediates in a Type I polyketide synthase can occur.

L37 ANSWER 3 OF 14 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2006042704 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16430229
TITLE: Heterologous production of epothilone C and D in Escherichia coli.
AUTHOR: Mutka Sarah C; Carney John R; Liu Yaoquan; Kennedy Jonathan
CORPORATE SOURCE: Kosan Biosciences, Inc., 3832 Bay Center Place, Hayward, California 94545, USA.
SOURCE: Biochemistry, (2006 Jan 31) Vol. 45, No. 4, pp. 1321-30. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200604
ENTRY DATE: Entered STN: 25 Jan 2006
Last Updated on STN: 15 Apr 2006
Entered Medline: 14 Apr 2006

AB The epothilones are a family of polyketide natural products that show a high potential as anticancer drugs. They are synthesized by the action of a hybrid nonribosomal peptide synthetase/polyketide synthase in the myxobacterium Sorangium cellulosum. In this work, the genes encoding the entire cluster,epoA, epoB, epoC, epoD, epoE, and epoF, were redesigned and synthesized to allow for expression in Escherichia coli. The expression of the largest of the proteins, EpoD, also required the protein be separated into two polypeptides with compatible module linkers. Using a combination of lowered temperature, chaperone coexpression, and alternative promoters, we succeeded in producing a soluble protein from all genes in the epothilone cluster. The entire synthetic epothilone cluster was then expressed in a strain of E. coli modified to enable polyketide biosynthesis, resulting in the production of epothilones C and D. Furthermore, feeding a thioester of the normal substrate for EpoD to cells expressing the epoD, epoE, and epoF genes also led to the production of epothilones C and D. The design of the synthetic epothilone genes together with E. coli expression provides the ideal platform for both the biochemical investigation of the epothilone PKS and the generation of novel biosynthetic epothilone analogues.

L37 ANSWER 4 OF 14 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2004583519 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15556004
TITLE: Hybrid nonribosomal peptide-polyketide interfaces in epothilone biosynthesis: minimal requirements at N and C termini of EpoB for elongation.
AUTHOR: Liu Fei; Garneau Sylvie; Walsh Christopher T
CORPORATE SOURCE: Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, 240 Longwood Avenue, Boston, MA 02115, USA.
CONTRACT NUMBER: GM21643 (NIGMS)
GM66456 (NIGMS)
SOURCE: Chemistry & biology, (2004 Nov) Vol. 11, No. 11, pp. 1533-42. Journal code: 9500160. ISSN: 1074-5521.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200504
ENTRY DATE: Entered STN: 24 Nov 2004
Last Updated on STN: 26 Apr 2005
Entered Medline: 25 Apr 2005

AB Epothilone (Epo) D, an antitumor agent currently in clinical trials, is a hybrid natural product produced by the combined action of nonribosomal peptide synthetases (NRPS) and polyketide

synthases (PKS). In the epothilone biosynthetic pathway, EpoB, a 165 kDa NRPS is inserted into an otherwise entirely PKS assembly line, forming two hybrid NRPS-PKS interfaces. In light of the terminal linker effect previously identified in PKS, the N- and C-terminal sequences of EpoB were examined for their roles in propagating the incipient natural product. Eight amino acid residues at EpoB C terminus, in which six are positively charged, were found to be a key component of the C-terminal linker effect. A minimal sequence of 56 residues at EpoB N terminus was required for elongating the acetyl group from the acyl carrier protein (ACP) of EpoA to form methylthiazolyl-S-EpoB.

L37 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:737868 CAPLUS Full-text
DOCUMENT NUMBER: 139:257289
TITLE: Methods to mediate polyketide synthase module effectiveness
INVENTOR(S): Gokhale, Rajesh S.; Tsuji, Stuart; Khosla, Chaitan; Wu, Nicholas; Cane, David E.
PATENT ASSIGNEE(S): The Board of Trustees of the Leland Stanford Junior University, USA; Brown University Research Foundation
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 2003076581 | A2 | 20030918 | WO 2003-US6910 | | 20030304 |
| WO 2003076581 | A3 | 20050210 | | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | | |
| US 2003068676 | A1 | 20030410 | US 2002-91244 | | 20020304 |
| US 7001748 | B2 | 20060221 | | | |
| AU 2003213757 | A1 | 20030922 | AU 2003-213757 | | 20030304 |
| US 2006110789 | A1 | 20060525 | US 2005-506630 | | 20050401 |
| PRIORITY APPLN. INFO.: | | | US 2002-361758P | P | 20020304 |
| | | | US 2002-91244 | A | 20020304 |
| | | | US 1999-119363P | P | 19990209 |
| | | | US 2000-500747 | A2 | 20000209 |
| | | | US 2001-272985P | P | 20010302 |
| | | | US 2001-272987P | P | 20010302 |
| | | | WO 2003-US6910 | W | 20030304 |

AB Linking sequences which modulate cross-talk between modules of Type I polyketide synthases have been identified. Thus, arbitrarily chosen modules can be mixed and matched by supplying the appropriate linkers to obtain desired polyketide synthases and new polyketides. The modules are provided suitable linkers so that the polyketide chain is passed from one module to the other in the correct sequence. Synthetic peptides which mimic linkers can be used to inhibit the synthesis of polyketides. Kinetic channeling, both intrapolypeptide and interpolypeptide, of diketide intermediates in a Type I polyketide synthase can occur. In addition, the role of protein-protein interactions between a donor acyl carrier protein (ACP) domain and a downstream ketosynthase (KS) domain and enzyme-substrate interactions in the channeling of intermediates between polyketide synthase modules and between a polyketide synthase module and a nonribosomal peptide synthase (NRPS) module has been identified.

L37 ANSWER 6 OF 14 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2003391751 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12888623
TITLE: Engineered biosynthesis of an ansamycin polyketide precursor in Escherichia coli.
AUTHOR: Watanabe Kenji; Rude Mathew A; Walsh Christopher T; Khosla Chaitan
CORPORATE SOURCE: Department of Chemical Engineering, Stanford University, Stanford, CA 94305, USA.
CONTRACT NUMBER: AI 77248 (NIAID)
GM 20011 (NIGMS)

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2003 Aug 19) Vol. 100, No. 17, pp. 9774-8. Electronic Publication: 2003-07-29. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T) (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 21 Aug 2003
Last Updated on STN: 30 Oct 2003
Entered Medline: 29 Oct 2003

AB Ansamycins such as rifamycin, ansamitocin, and geldanamycin are an important class of polyketide natural products. Their biosynthetic pathways are especially complex because they involve the formation of 3-amino-5-hydroxybenzoic acid (AHBA) followed by backbone assembly by a hybrid nonribosomal peptide synthetase/polyketide synthase. We have reconstituted the ability to synthesize 2,6-dimethyl-3,5,7-trihydroxy-7-(3'-amino-5'-hydroxyphenyl)-2,4- heptadienoic acid (P8/1-OG), an intermediate in rifamycin biosynthesis, in an extensively manipulated strain of Escherichia coli. The parent strain, BAP1, contains the sfp phosphopantetheinyl transferase gene from Bacillus subtilis, which posttranslationally modifies polyketide synthase and nonribosomal peptide synthetase modules. AHBA biosynthesis in this host required introduction of seven genes from Amycolatopsis mediterranei, which produces rifamycin, and Actinosynnema pretiosum, which produces ansamitocin. Because the four-module RifA protein (530 kDa) from the rifamycin synthetase could not be efficiently produced in an intact form in E. coli, it was genetically split into two bimodular proteins separated by matched linker pairs to facilitate efficient inter-polypeptide transfer of a biosynthetic intermediate. A derivative of BAP1 was engineered that harbors the AHBA biosynthetic operon, the bicistronic RifA construct and the pccB and accA1 genes from Streptomyces coelicolor, which enable methylmalonyl-CoA biosynthesis. Fermentation of this strain of E. coli yielded P8/1-OG, an N-acetyl P8/1-OG analog, and AHBA. In addition to providing a fundamentally new route to shikimate and ansamycin-type compounds, this result enables further genetic manipulation of AHBA-derived polyketide natural products with unprecedented power.

L37 ANSWER 7 OF 14 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2003154756 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12670230
TITLE: Intermodular communication in modular polyketide synthases: structural and mutational analysis of linker mediated protein-protein recognition.
AUTHOR: Kumar Pawan; Li Qing; Cane David E; Khosla Chaitan
CORPORATE SOURCE: Department of Chemical Engineering, Stanford University, Stanford, California 94305, USA.
CONTRACT NUMBER: CA66736 (NCI)
GM 22172 (NIGMS)
SOURCE: Journal of the American Chemical Society, (2003 Apr 9) Vol. 125, No. 14, pp. 4097-102. Journal code: 7503056. ISSN: 0002-7863.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 3 Apr 2003
Last Updated on STN: 20 May 2003
Entered Medline: 19 May 2003

AB Modular polyketide synthases (PKSs) present an attractive scaffold for the engineered biosynthesis of novel polyketide products via recombination of naturally occurring enzyme modules with desired catalytic properties. Recent studies have highlighted the pivotal role of short intermodular "linker pairs" in the selective channeling of biosynthetic intermediates between adjacent PKS modules. Using a combination of computer modeling, NMR spectroscopy, cross-linking, and site-directed mutagenesis, we have investigated the mechanism by which a linker pair from the 6-deoxyerythronolide B synthase promotes chain transfer. Our studies support a "coiled-coil" model in which the individual peptides comprising this linker pair adopt helical conformations that associate through a combination of hydrophobic and electrostatic interactions in an antiparallel fashion. Given the important contribution of such linker pair interactions to the kinetics of chain transfer between PKS modules, the ability to rationally modulate linker pair affinity by site-directed mutagenesis could be useful in the construction of optimized hybrid PKSs.

L37 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:909234 CAPLUS Full-text
DOCUMENT NUMBER: 140:37748

TITLE: Challenges to combinatorial biosynthesis. Substrate specificity of hybrid multimodular synthases produced by polyketide synthase gene
AUTHOR(S): Watanabe, Kenji
CORPORATE SOURCE: Graduate School of Agriculture, Hokkaido University, Japan
SOURCE: Kagaku to Seibutsu (2003), 41(11), 753-756
CODEN: KASEAA; ISSN: 0453-073X
PUBLISHER: Gakkai Shuppan Senta
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review on studies of the substrate specificity of polyketide synthase modules and production of hybrid multimodular synthases by combination of the modules and selection of polypeptide linkers for combinatorial biosynthesis of various polyketides.

L37 ANSWER 9 OF 14 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2002207064 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11939803
TITLE: Quantitative analysis of the relative contributions of donor acyl carrier proteins, acceptor ketosynthases, and linker regions to intermodular transfer of intermediates in hybrid polyketide synthases.
AUTHOR: Wu Nicholas; Cane David E; Khosla Chaitan
CORPORATE SOURCE: Department of Chemistry, Stanford University, Stanford, California 94305, USA.
CONTRACT NUMBER: CA66736 (NCI)
GM22172 (NIGMS)
SOURCE: Biochemistry, (2002 Apr 16) Vol. 41, No. 15, pp. 5056-66.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 10 Apr 2002
Last Updated on STN: 18 May 2002
Entered Medline: 17 May 2002
AB 6-Deoxyerythronolide B synthase (DEBS) is the modular polyketide synthase (PKS) responsible for the biosynthesis of 6-dEB, the aglycon core of the antibiotic erythromycin. The biosynthesis of 6-dEB proceeds in an assembly-line fashion through the six modules of DEBS, each of which catalyzes a dedicated set of reactions, such that the structure of the final product is determined by the arrangement of modules along the assembly line. This transparent relationship between protein sequence and enzyme function is common to all modular PKSs and makes these enzymes an attractive scaffold for protein engineering through module swapping. One of the fundamental issues relating to module swapping that still needs to be addressed is the mechanism by which intermediates are channeled from one module to the next. While it has been previously shown that short linker regions at the N- and C-termini of adjacent polypeptides play an important role in mediating intermodular transfer, the contributions of other protein-protein interactions have not yet been probed. Here, we investigate the roles of the linker interactions as well as the interactions between the donor acyl carrier protein (ACP) domain and the downstream ketosynthase (KS) domain in various contexts. Linker interactions and ACP-KS interactions make relatively equal contributions at the module 2-module 3 and the module 4-module 5 interfaces in DEBS. In contrast, modules 2 and 6 are more tolerant toward substrates presented by nonnatural ACP domains. This tolerance was exploited for engineering hybrid PKS-PKS and PKS-NRPS (nonribosomal peptide synthetase) junctions and suggests fundamental ground rules for engineering novel chimeric PKSs in the future.

L37 ANSWER 10 OF 14 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2002177295 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11908996
TITLE: Cloning and characterization of the bleomycin biosynthetic gene cluster from Streptomyces verticillus ATCC15003.
AUTHOR: Shen Ben; Du Liangcheng; Sanchez Cesar; Edwards Daniel J; Chen Mei; Murrell Jeffrey M
CORPORATE SOURCE: Department of Chemistry, University of California, Davis, One Shields Avenue, Davis, California 95616, USA..
bshen@pharmacy.wisc.edu
CONTRACT NUMBER: AI40475 (NIAID)
GM07377 (NIGMS)

SOURCE: Journal of natural products, (2002 Mar) Vol. 65, No. 3, pp. 422-31. Ref: 35
Journal code: 7906882. ISSN: 0163-3864.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 24 Mar 2002
Last Updated on STN: 12 Jun 2002
Entered Medline: 11 Jun 2002

AB Bleomycin (BLM) biosynthesis has been studied as a model for hybrid peptide-polyketide natural product biosynthesis. Cloning, sequencing, and biochemical characterization of the blm biosynthetic gene cluster from Streptomyces verticillus ATCC15003 revealed that (1) the BLM hybrid peptide-polyketide aglycon is assembled by the BLM megasynthetase that consists of both nonribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) modules; (2) BlmIX/BlmVIII/BlmVII constitute a natural hybrid NRPS/PKS/NRPS system, serving as a model for both hybrid NRPS/PKS and PKS/NRPS systems; (3) the catalytic sites appear to be conserved in both hybrid NRPS/PKS and nonhybrid NRPS or PKS systems, with the exception of the KS domains in the hybrid NRPS/PKS systems that are unique; (4) specific interpolypeptide linkers may play a critical role in intermodular communication to facilitate the transfer of the growing intermediates between the interacting NRPS and/or PKS modules; (5) post-translational modification of the BLM megasynthetase has been accomplished by a single PPTase with broad carrier protein specificity; and (6) BlmIV/BlmIII-templated assembly of the BLM bithiazole moiety requires intriguing protein juxtaposition and modular recognition. These results lay the foundation to investigate the molecular basis for intermodular communication between NRPS and PKS in hybrid peptide-polyketide natural product biosynthesis and set the stage for engineering novel BLM analogues by genetic manipulation of genes governing BLM biosynthesis.

L37 ANSWER 11 OF 14 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2002051155 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11774003
TITLE: The biosynthetic gene cluster for the anticancer drug bleomycin from Streptomyces verticillus ATCC15003 as a model for hybrid peptide-polyketide natural product biosynthesis.
AUTHOR: Shen B; Du L; Sanchez C; Edwards D J; Chen M; Murrell J M
CORPORATE SOURCE: Department of Chemistry, University of California, Davis, One Shields Avenue, Davis, CA 95616, USA.
CONTRACT NUMBER: AI40475 (NIAID)
T32GM07377 (NIGMS)
SOURCE: Journal of industrial microbiology & biotechnology, (2001 Dec) Vol. 27, No. 6, pp. 378-85. Ref: 31
Journal code: 9705544. ISSN: 1367-5435.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 25 Jan 2002
Last Updated on STN: 21 Feb 2002
Entered Medline: 20 Feb 2002

AB The hybrid peptide-polyketide backbone of bleomycin (BLM) is assembled by the BLM megasynthetase that consists of both nonribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) modules. BlmIX/BlmVIII/BlmVII constitute a natural hybrid NRPS/PKS/NRPS system, serving as a model for both hybrid NRPS/PKS and PKS/NRPS systems. Sequence analysis and functional comparison of domains and modules of BlmIX/BlmVIII/BlmVII with those of nonhybrid NRPS and PKS systems suggest that (1) the same catalytic sites appear to be conserved in both hybrid NRPS-PKS and nonhybrid NRPS or PKS systems, with the exception of the KS domains in the hybrid NRPS/PKS systems that are unique; (2) specific interpolypeptide linkers may play a critical role in intermodular communication to facilitate transfer of the growing intermediates between the interacting NRPS and/or PKS modules; and (3) posttranslational modification of the BLM megasynthetase has been accomplished by a single PPTase with a broad substrate specificity toward the apo forms of both acyl carrier proteins (ACPs) and peptidyl carrier proteins (PCPs).

L37 ANSWER 12 OF 14 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2001293979 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 11378961
TITLE: Biosynthesis of hybrid peptide-polyketide natural products.
AUTHOR: Du L; Shen B
CORPORATE SOURCE: Department of Chemistry, University of California at Davis, One Shields Avenue, Davis, CA 95616, USA.. shen@chem.ucdavis.edu
CONTRACT NUMBER: AI40475 (NIAID)
CA78747 (NCI)
SOURCE: Current opinion in drug discovery & development, (2001 Mar) Vol. 4, No. 2, pp. 215-28. Ref: 56
Journal code: 100887519. ISSN: 1367-6733.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 22 Oct 2001
Last Updated on STN: 22 Oct 2001
Entered Medline: 18 Oct 2001

AB The structural and catalytic similarities between non-ribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) support the idea of combining individual NRPS and PKS modules for combinatorial biosynthesis. Recent advances in cloning and characterization of biosynthetic gene clusters for naturally occurring hybrid polyketide-peptide metabolites have provided direct evidence for the existence of hybrid NRPS-PKS systems, thus setting the stage to investigate the molecular basis for intermodular communication between NRPS and PKS modules. Reviewed in this article are biosynthetic data pertinent to hybrid peptide-polyketide biosynthesis published up to late 2000. Hybrid peptide-polyketide natural products can be divided into two classes: (i) those whose biosyntheses do not involve functional interaction between NRPS and PKS modules; and (ii) those whose biosyntheses are catalyzed by hybrid NRPS-PKS systems involving direct interactions between NRPS and PKS modules. It is the latter systems that are most likely amenable to combinatorial biosynthesis. The same catalytic sites appear to be conserved in both hybrid NRPS-PKS and normal NRPS or PKS systems, with the exception of the ketoacyl synthase domains in hybrid NRPS-PKS systems which are unique. Specific linkers may play a critical role in communication, facilitating the transfer of the growing intermediates between the interacting NRPS and/or PKS modules. In addition, phosphopantetheinyl transferases with broad carrier protein specificity are essential for the production of functional hybrid NRPS-PKS megasynthetases. These findings should now be taken into consideration in engineered biosynthesis of hybrid peptide-polyketide natural products for drug discovery and development.

L37 ANSWER 13 OF 14 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2001301512 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11162234
TITLE: Hybrid peptide-polyketide natural products: biosynthesis and prospects toward engineering novel molecules.
AUTHOR: Du L; Sanchez C; Shen B
CORPORATE SOURCE: Department of Chemistry, University of California, One Shields Avenue, Davis, California 95616, USA.
CONTRACT NUMBER: AI40475 (NIAID)
CA78747 (NCI)
SOURCE: Metabolic engineering, (2001 Jan) Vol. 3, No. 1, pp. 78-95.
Ref: 66
Journal code: 9815657. ISSN: 1096-7176.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 4 Jun 2001
Last Updated on STN: 4 Jun 2001
Entered Medline: 31 May 2001

AB The structural and catalytic similarities between modular nonribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) inspired us to search for hybrid NRPS-PKS systems. By examining the biochemical and genetic data known to date for the biosynthesis of hybrid peptide-polyketide natural products, we show (1) that the same catalytic sites are conserved between the hybrid NRPS-PKS and normal NRPS or PKS systems, although the ketoacyl synthase domain in NRPS/PKS hybrids is

unique, and (2) that specific interpolypeptide linkers exist at both the C- and N-termini of the NRPS and PKS proteins, which presumably play a critical role in facilitating the transfer of the growing peptide or polyketide intermediate between NRPS and PKS modules in hybrid NRPS-PKS systems. These findings provide new insights for intermodular communications in hybrid NRPS-PKS systems and should now be taken into consideration in engineering hybrid peptide-polyketide biosynthetic pathways for making novel "unnatural" natural products.


L37 ANSWER 14 OF 14 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 1999439949 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10508677
TITLE: Knowledge-based design of bimodular and trimodular polyketide synthases based on domain and module swaps: a route to simple statin analogues.
AUTHOR: Ranganathan A; Timoney M; Bycroft M; Cortes J; Thomas I P; Wilkinson B; Kellenberger L; Hanefeld U; Galloway I S; Staunton J; Leadlay P F
CORPORATE SOURCE: Cambridge Centre for Molecular Recognition, Department of Biochemistry, University of Cambridge, Tennis Court Road, Cambridge, CB2 1GA, UK.
SOURCE: Chemistry & biology, (1999 Oct) Vol. 6, No. 10, pp. 731-41. Journal code: 9500160. ISSN: 1074-5521.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 11 Jan 2000
Last Updated on STN: 11 Jan 2000
Entered Medline: 24 Nov 1999

AB BACKGROUND: Polyketides are structurally diverse natural products that have a range of medically useful activities. Nonaromatic bacterial polyketides are synthesised on modular polyketide synthase (PKS) multienzymes, in which each cycle of chain extension requires a different 'module' of enzymatic activities. Attempts to design and construct modular PKSs that synthesise specified novel polyketides provide a particularly stringent test of our understanding of PKS structure and function. RESULTS: We have constructed bimodular and trimodular PKSs based on DEBS1-TE, a derivative of the erythromycin PKS that contains only modules 1 and 2 and a thioesterase (TE), by substituting multiple domains with appropriate counterparts derived from the rapamycin PKS. Hybrid PKSs were obtained that synthesised the predicted target triketide lactones, which are simple analogues of cholesterol-lowering statins. In constructing intermodular fusions, whether between modules in the same or in different proteins, it was found advantageous to preserve intact the acyl carrier protein-ketosynthase (ACP-KS) didomain that spans the junction between successive modules. CONCLUSIONS: Relatively simple considerations govern the construction of functional hybrid PKSs. Fusion sites should be chosen either in the surface-accessible linker regions between enzymatic domains, as previously revealed, or just inside the conserved margins of domains. The interaction of an ACP domain with the adjacent KS domain, whether on the same polyketide or not, is of particular importance, both through conservation of appropriate protein-protein interactions, and through optimising molecular recognition of the altered polyketide chain in the key transfer of the acyl chain from the ACP of one module to the KS of the downstream module.

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